NICE National Institute for Health and Care Excellence

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Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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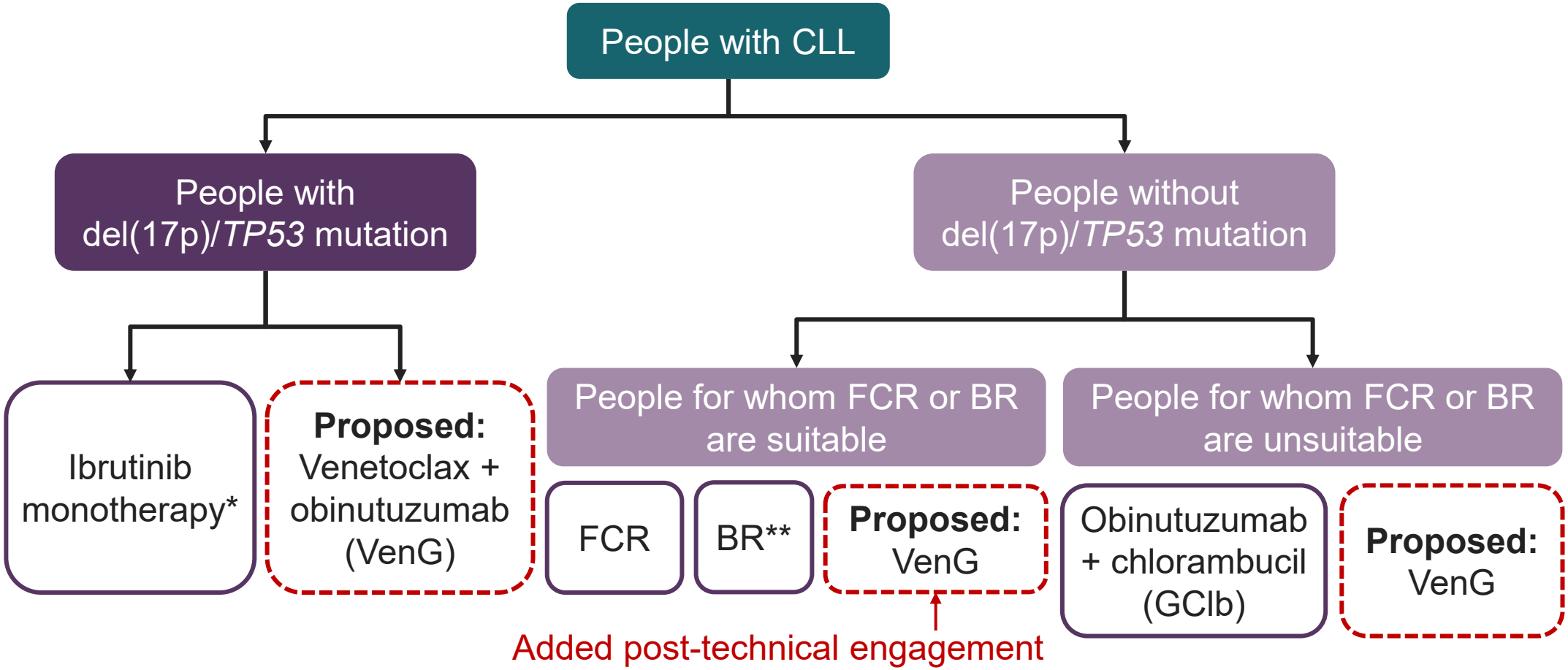
Company: AbbVie

ACM 1 4th August 2020

Chronic lymphocytic leukaemia

- CLL is the most common of the chronic leukaemias, comprising 30% of all adult leukaemia. In England there were 3,157 new cases of CLL in 2017.
- 5-year relative survival rates are around 70% and 75% for men and women, respectively.
- Treatment options for untreated CLL depend on factors such as stage of disease, performance status and co-morbidities. Most people will not have symptoms when first diagnosed, and in this case will not need any treatment.
- Around 5% to 10% of people with CLL have ‘high-risk’ disease, characterised by the presence of 17p deletion or *TP53* mutation. This can increase the rate of cell growth and resistance to chemoimmunotherapy, significantly reducing overall survival.
- Immunoglobulin heavy chain variable region (IGHV) mutations are found in around 60% of newly diagnosed and asymptomatic CLL patients. IGHV-mutated CLL is associated with a better prognosis, and is a powerful predictor of duration of response and overall survival with chemoimmunotherapy.

Treatment pathway: untreated CLL



* NICE recommends idelalisib with rituximab for people with del(17p)/*TP53* mutation, but clinical experts agree that it has now been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab

** Only if FCR is unsuitable

FCR = Fludarabine, cyclophosphamide and rituximab

BR = Bendamustine and rituximab

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Venetoclax (Venclyxto, AbbVie)

Marketing authorisation	• Venetoclax in combination with obinutuzumab for treating adults with previously untreated CLL (received March 2020)
Mechanism of action	• **Venetoclax:** Selective inhibitor of B-cell lymphoma 2 (Bcl2) • **Obinutuzumab:** Anti-CD20 monoclonal antibody

Administration	• **Venetoclax** is taken orally, once daily. Dose escalates from 20mg per day to 400mg per day over 5 weeks. Venetoclax is taken for 12 x 28-day cycles
	• **Obinutuzumab** is administered intravenously for 6, 28-day cycles:
	  • 1,000mg on Days 1, 8 and 15 of Cycle 1 (the first 1,000-mg dose may be split over Days 1 and 2)
	  • 1,000mg on Day 1 of Cycles 2–6

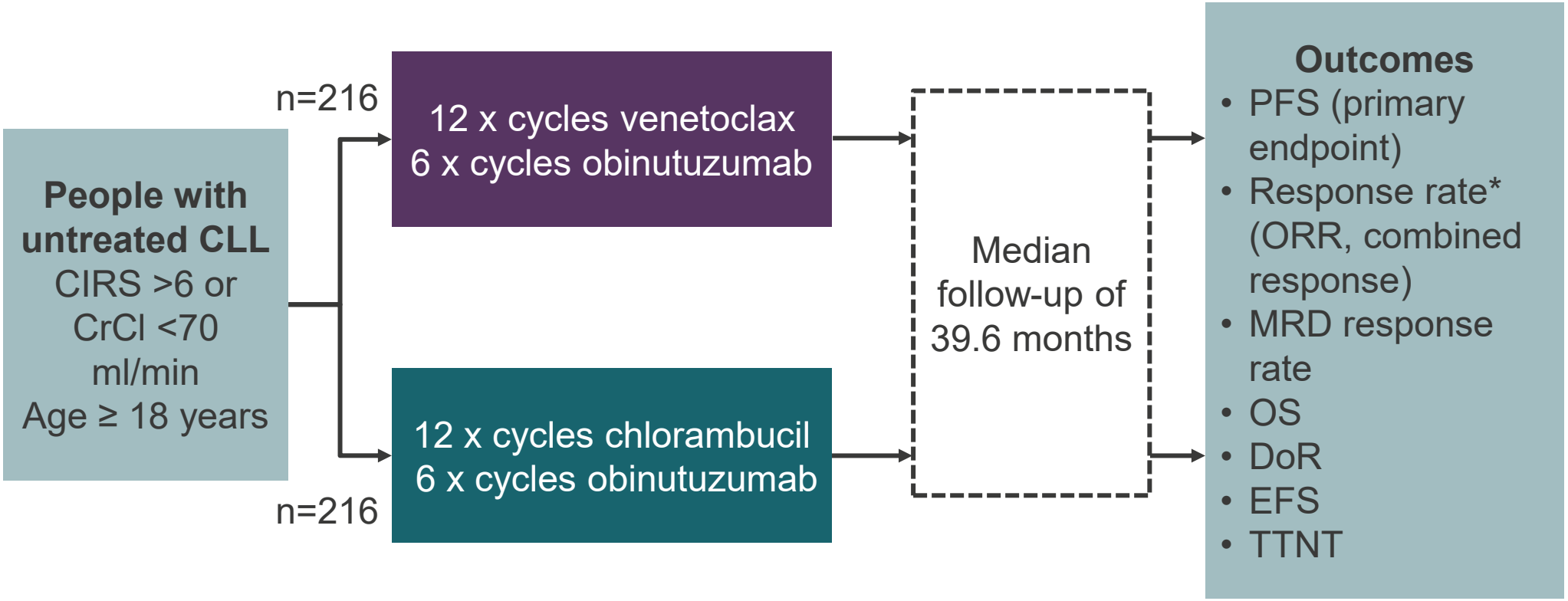
Price	• **Venetoclax:** £4,789.47 for a pack of 112 x 100-mg tablets (list price). **Obinutuzumab:** £3,312.00 for a 1,000-mg vial for infusion (list price). • The average cost of a 1-year treatment course with venetoclax in combination with obinutuzumab is [redacted] (list price) • Simple PAS discounts have been approved for venetoclax and obinutuzumab

Submission summary

Subgroups and comparators: people with previously untreated CLL	1) People without del(17p)/*TP53* mutation, for whom FCR or BR are unsuitable. **Comparator:** GClb 2) People with del(17p)/*TP53* mutation. **Comparator:** ibrutinib 3) People for whom FCR or BR are suitable. **Comparators:** FCR and BR
Clinical trial	**CLL14:** phase 3, open-label, parallel, multicentre randomised controlled trial comparing VenG with GClb. N=432 people with untreated CLL in total (N=49 with del(17p)/*TP53* mutation)
Key CLL14 results vs. GClb (Subgroup 1)	**PFS HR:** 0.31 in favour of VenG (95% CI 0.22 to 0.44), p<0.001 **Median PFS:** Not reached (VenG), 35.6 months (GClb) **OS HR:** 1.03 in favour of GClb (95% CI 0.60 to 1.75), p=0.921 **Median OS:** Not reached in either treatment arm **TTNT HR:** 0.51 in favour of VenG (95% CI 0.34 to 0.78), p=0.012 **Median TTNT:** Not reached in either treatment arm
ITC results vs. ibrutinib (Subgroup 2)	**PFS HR:** 1.515 in favour of ibrutinib (95% CI 0.619 to 3.704), p=0.363 **OS HR:** 1.189 in favour of ibrutinib (95% CI 0.425 to 3.322), p=0.741
ITC results vs. FCR/BR (Subgroup 3)	**PFS HR**: 0.258 in favour of VenG vs FCR (95% CI 0.151 to 0.481); 0.178 in favour of VenG vs BR (95% CI 0.109 to 0.312) **OS HR:** 0.622 in favour of VenG vs FCR (95% CI 0.273 to 1.789); 0.792 in favour of VenG vs BR (95% CI 0.378 to 1.969)

TTNT = Time to next treatment

CLL14 (n=432)
Open label, randomised controlled trial

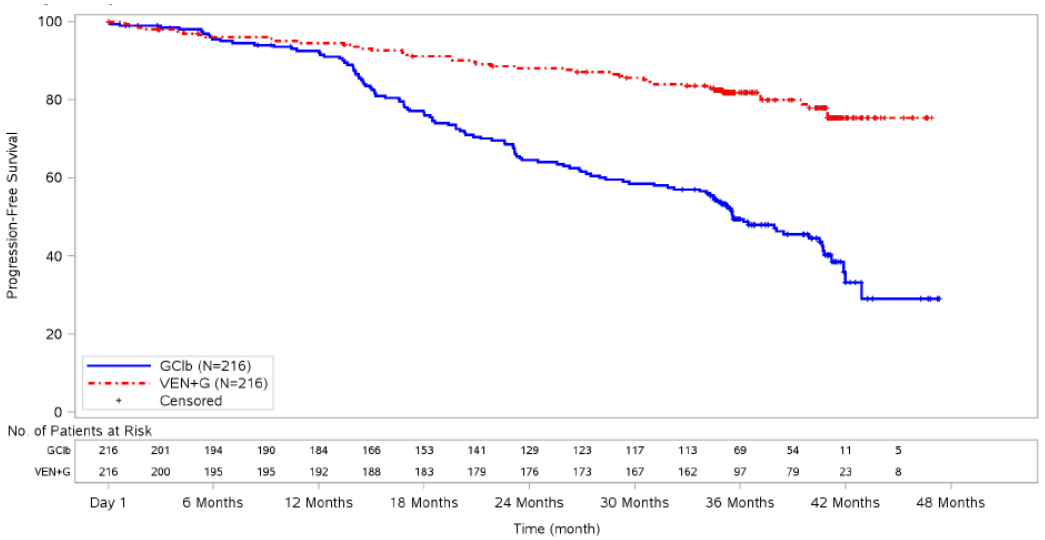


* Assessed at end of treatment

CIRS = Cumulative illness rating scale; CrCl = Creatinine clearance;
DoR = Duration of response; EFS = Event-free survival; MRD = Minimal residual disease;
PFS = Progression-free survival; ORR = Overall response rate; OS = Overall survival

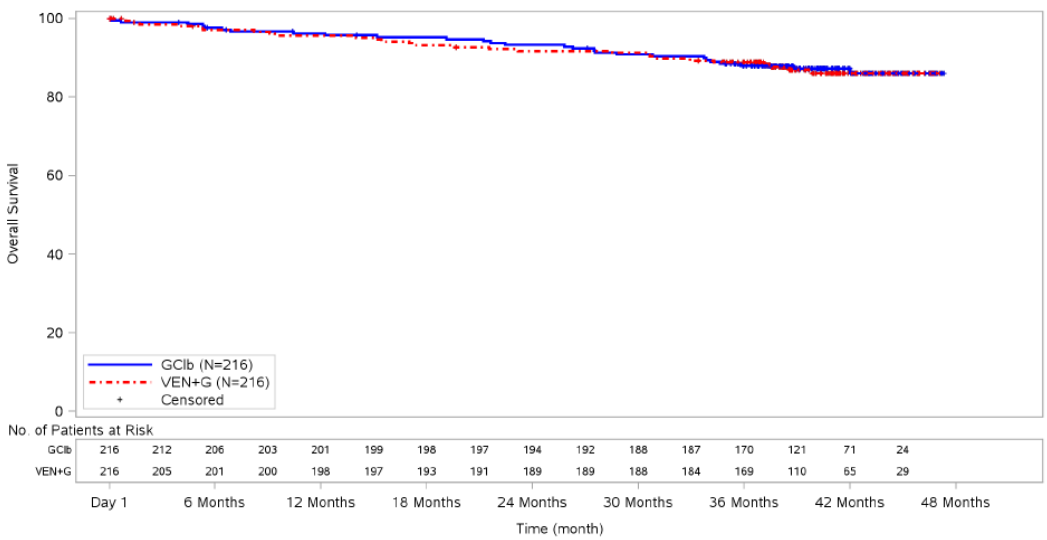
CLL14: PFS and OS results

Progression-free survival



	VenG (n=216)	GClb (n=216)
Events	[redacted]	[redacted]
Median	Not reached	35.6 months
1-year KM	[redacted]	[redacted]
2-year KM	88.2%	64.1%
3-year KM	81.9%	49.5%
HR	0.31 (0.22 – 0.44)	

Overall survival



	VenG (n=216)	GClb (n=216)
Events	[redacted]	[redacted]
Median	Not reached	Not reached
1-year KM	[redacted]	[redacted]
2-year KM	91.8%	93.3%
3-year KM	88.9%	88.0%
HR	1.03 (0.60 – 1.75)	

Overview of indirect treatment comparison with ibrutinib (people with del(17p)/*TP53* mutation)

- 25 patients from the VenG arm in CLL14 had del(17p)/*TP53* mutation
- 3 studies presented data for ibrutinib in the subgroup of interest. 1 was excluded due to small sample size with del(17p). MAIC not possible due to small sample sizes
- Possible confounding factors for the remaining 2 studies include:
  1. the lack of information reported on baseline prognostic factors
  2. study populations were likely to be younger and fitter than CLL14
  3. lack of adjustment made for population heterogeneity
  4. Kaplan-Meier curves were digitised, increasing uncertainty

	Mato, 2018	Ahn, 2018
Design	Real-world evidence	Phase 2 single arm
Number of patients with del(17p)/*TP53* mutation	110	34

Company and ERG base case due to larger patient numbers

Overview of network meta-analysis with FCR/BR (people for whom FCR or BR are suitable)

- 9 studies were included in a network connecting VenG with FCR and BR. FCR and BR trials included either only ‘fit’ or ‘unfit’ patients, and were compared with the VenG data from CLL14 (which includes only ‘unfit’ patients, and some with del(17p)/*TP53* mutation)

NMA = Network meta-analysis

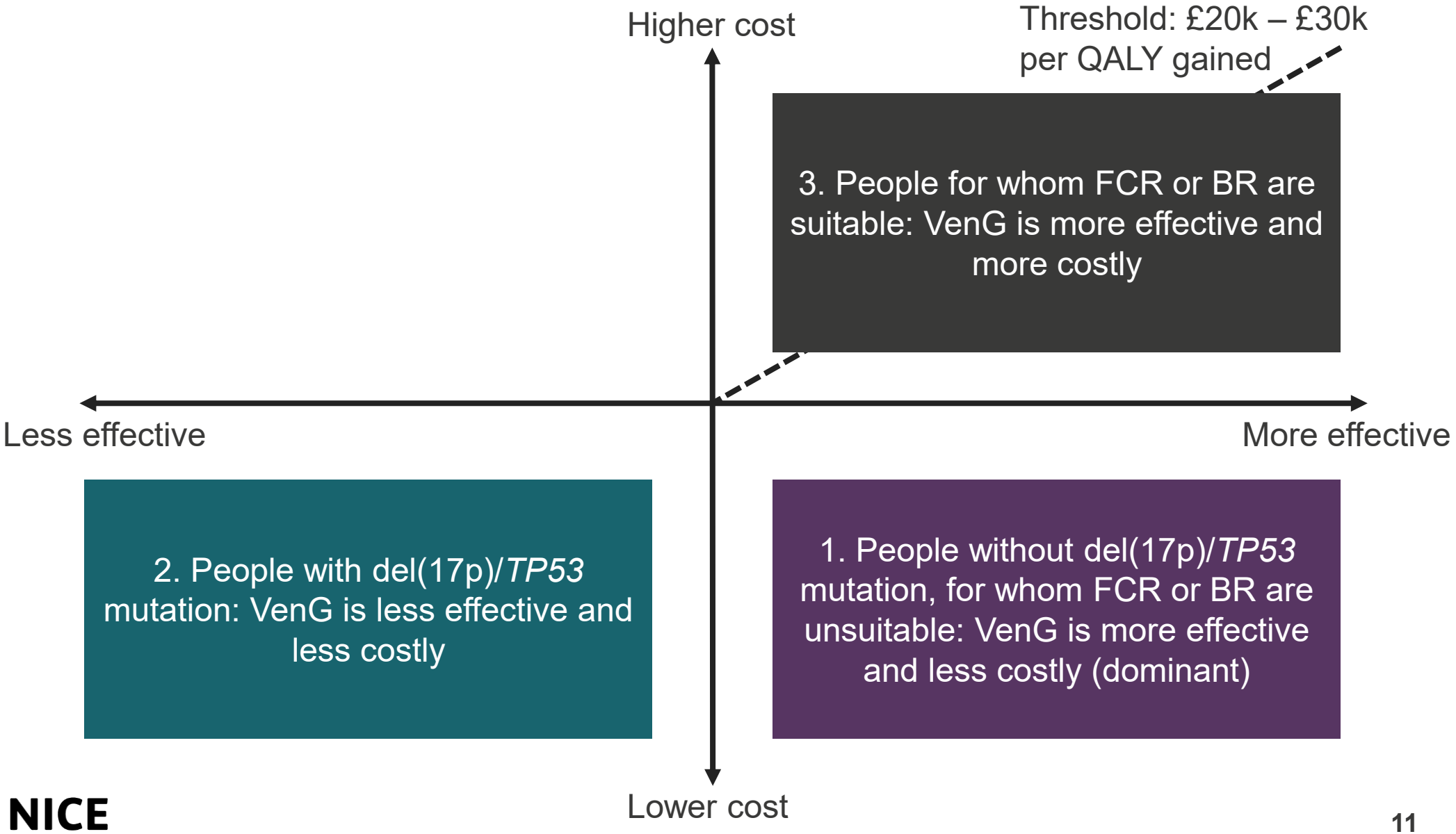
Summary of cost-effectiveness results

Model	Partitioned survival model, 3 health states: progression-free, progressed disease, death
Company cost-effectiveness results by subgroup*	**1. People without del(17p)/*TP53* mutation, for whom FCR/BR are unsuitable**
	ICER (vs. GClb): Dominant NMB at WTP threshold of £20k/QALY: £152,904, £30k/QALY: £161,081
	2. People with del(17p)/*TP53* mutation
	ICER (vs. ibrutinib): £799,551 per QALY foregone (south west ICER) NMB at WTP threshold of £20k/QALY: £273,870, £30k/QALY: £270,357
	3. People for whom FCR or BR are suitable
	vs FCR: ICER: £32,669/QALY; vs BR: ICER: £36,768/QALY
Technical team-preferred results by subgroup*	**1. People without del(17p)/*TP53* mutation, for whom FCR/BR are unsuitable**
	ICER: Dominant NMB at WTP threshold of £20k/QALY: £154,888, £30k/QALY: £159,432
	2. People with del(17p)/*TP53* mutation
	ICER: £628,912 per QALY foregone (south west ICER) NMB at WTP threshold of £20k/QALY: £221,125, £30k/QALY: £217,493
	3. People for whom FCR or BR are suitable
	vs FCR: ICER: £47,494/QALY; vs BR: ICER: £67,445/QALY

* venetoclax PAS price, applying the ERG-preferred pre-progression off-treatment utility

NMB = Net monetary benefit
WTP = Willingness to pay

VenG has a lower cost than comparators in 2 of the subgroups over the model time horizon



Decision-making with south west quadrant ICERs

- South-west quadrant ICERs are presented as costs saved per QALY lost.
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
  - this is reflected in decision making in previous appraisals with south-west quadrant ICERs (e.g. TA433, TA561).
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss.
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost.
- As with other decision-making, more certainty is needed the closer to the margins of cost-effectiveness the ICERs are.

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team
1	**Relevance of population for whom FCR or BR are suitable:** initially excluded from the company submission, but a comparison of VenG with FCR and BR has been provided as a response to technical engagement	Patients for whom FCR or BR are suitable are a relevant population. It is likely that FCR or BR therapy would be suitable for some CLL14 patients in UK clinical practice. There is also an unmet need and VenG likely has superior efficacy to FCR/BR	Patients for whom FCR or BR are suitable are a relevant population
7	**Pre-progression off-treatment utility:** ERG considers the company's utility from TA343 (0.82) too high, and derived an age-matched utility from the general population (0.77)	Agree with the ERG's revised value of 0.77	The ERG's utility of 0.77 is more plausible
8	**Quality of life impact of VenG:** [redacted]	VenG has a quality of life benefit due to reduced long-term toxicity and rapid remission that was difficult to capture in CLL14	The expert submissions strongly support a quality of life benefit for VenG

Key issues

- Resolved at technical engagement (see previous slide)
- For discussion: low/moderate ICER impact
- For discussion: large ICER impact

Issue	Company base case	Technical team
1. Population	Subgroup 3 omitted initially	Subgroup 3 is a relevant population
2,3,4b. Extrapolations: Subgroup 1	PFS: Independent log-logistic	PFS: The ERG's 2-knot hazard spline model aligns better with observed data in CLL11
	OS: Dependent exponential	OS: Clinical opinion is mixed, but on balance supports the company's model
	TTNT: Independent log-logistic	TTNT: The ERG's TTNT model is preferred as it is closer to the ERG's PFS model
4a. Subseq. tx costs: Subgroups 1, 2	Costs apply from start of second-line treatment until death	Costs will fall between company base case and scenario where costs are constrained to 2L tx
5. ITC HRs: Subgroup 2	Applies the hazard ratios based on Mato	Clinical opinion supports the Mato comparison
6. Extrapolations: Subgroup 2	PFS: Independent log-logistic	The ERG's model is more plausible
	OS: Dependent exponential	The ERG's model is more plausible
7. Utilities	Applied pre-progression, off-treatment utility of 0.82	The ERG's revised utility of 0.77 is more plausible
8. VenG QoL impact	VenG improves efficacy without compromising QoL	Clinical input suggests VenG positively impacts QoL, but this was difficult to capture in CLL14
9. ITC HRs: Subgroup 3	Applies the PFS and OS HRs from the network meta analysis	The ERG's revised hazard ratios are preferred, though there is substantial uncertainty

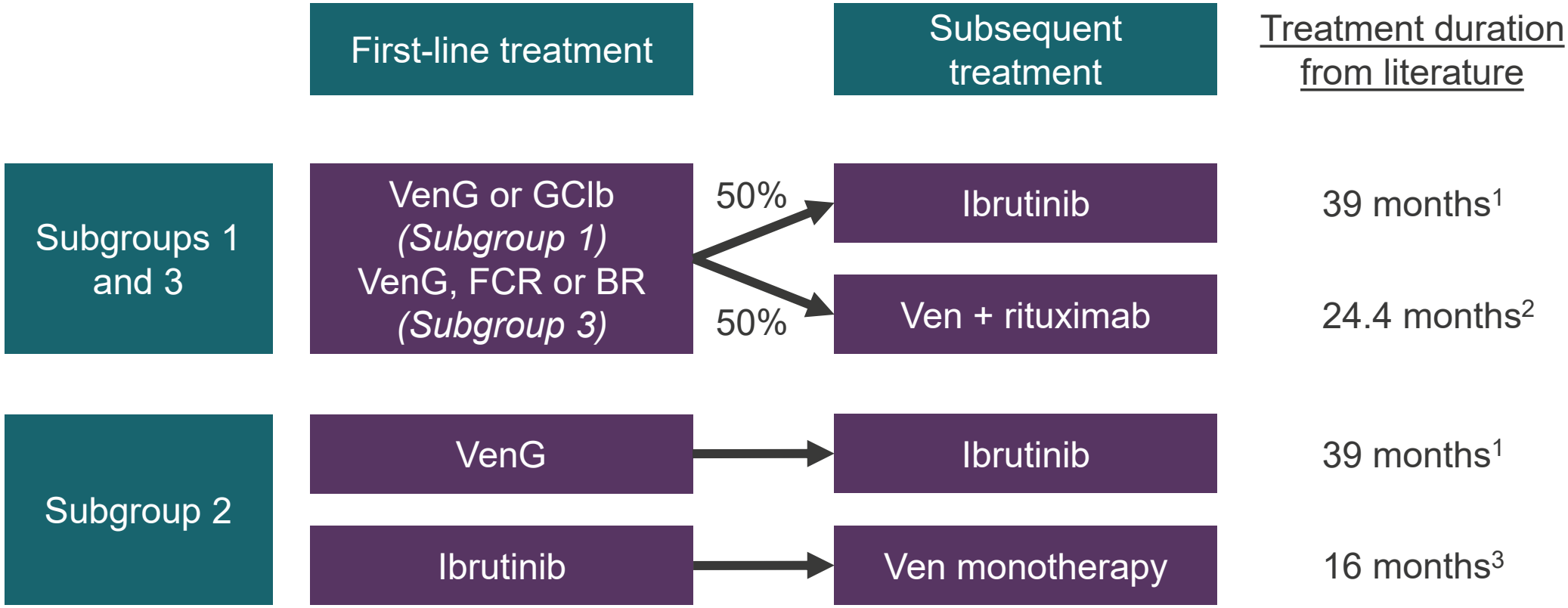
The post-progression state is associated with large subsequent treatment costs

Model structure

Progression-free	Post-progression*	Death
Key costs		
• 12 months of first-line treatment (VenG or GClb)	• Costs of subsequent treatment (ibrutinib, venetoclax + rituximab or venetoclax) from start of second-line treatment until death	• One-off cost associated with terminal care
Utilities applied		
• 12 months of 'pre-progression receiving IV treatment' utility (0.670) • Higher 'pre-progression off-treatment' utility (ERG: value of 0.77) applied thereafter until progression	• Post-progression utility of 0.60 applied	• Not applicable

* For ibrutinib, FCR and BR, only new incidences of either progression or death per cycle are counted towards subsequent treatment costs

The subsequent treatment mix applied in the model depends on the first-line treatment



The subsequent treatment durations inputted into the company's base-case model modify the average cost per cycle for subsequent treatment, but do not affect how long these costs are applied for

1. Kater et al. (2019): MURANO trial; 2. O'Brien et al. (2018); 3. Davids et al. (2018)

Patient and professional group comments

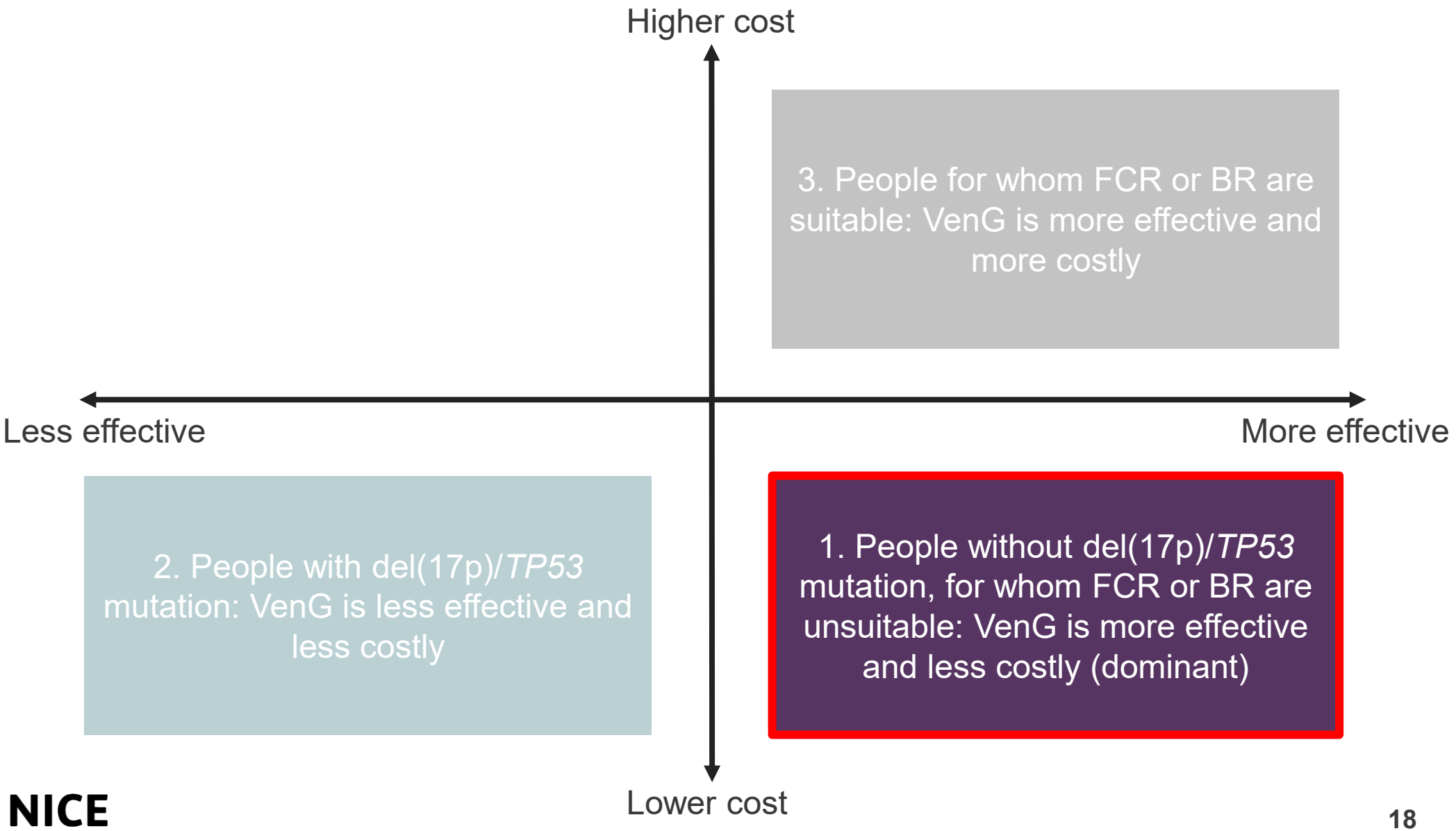
Patients

- Severe psychological impact: shock at diagnosis, long time spent with significant symptoms in “watch and wait” stage, expectations of relapse.
- Family and social life impacted: due to compromised immune system. ‘Ripple effect’ on family - caretaking duties and financial impact.
- In older patients, many treatments may not be tolerated with subsequent poor response with additional treatments.
- *“Living with CLL is living with uncertainty for both the patient and carer”.*

Professional comments

- High unmet need evident, poor PFS and OS when treated with current treatment options.
- Patterns of relapse and progression or unacceptable toxicity with some treatment options.
- The time-limited nature of VenG treatment is important to patients, as it has an improved tolerability profile and QoL benefit over current treatment options.

Issues for discussion: Subgroup 1



Issue 2: Progression-free survival extrapolations

- **ERG:** the company's log-logistic PFS model overestimates 3-year PFS for GClb compared to 1) the 3-year data from CLL11, CLL14 and ERIC, 2) the ERG's clinical expert, and 3) the 5-year data from CLL11
- The company's model also overestimates mean PFS duration versus TA343 (GClb for untreated CLL)
- The ERG favours a 2-knot hazard spline model, which is not dependent on background mortality, unlike the company's log-logistic model
- **Company**: there are differences between CLL14, CLL11 and ERIC in patient populations and trial design. The CLL11 PFS results include patients with del(17p)/*TP53* mutation, and are therefore likely to be lower
- The PFS curves are naturally expected to meet the rates of general population mortality, given the expected age and comorbidities of the population
- Clinical experts confirmed that ~10% of their GClb patients were in PFS at 10 years, compared to [redacted] stated by the ERG's expert
- **Expert submissions:** the ERG's PFS curve is more plausible, as it is more closely aligned with the observed CLL11 data

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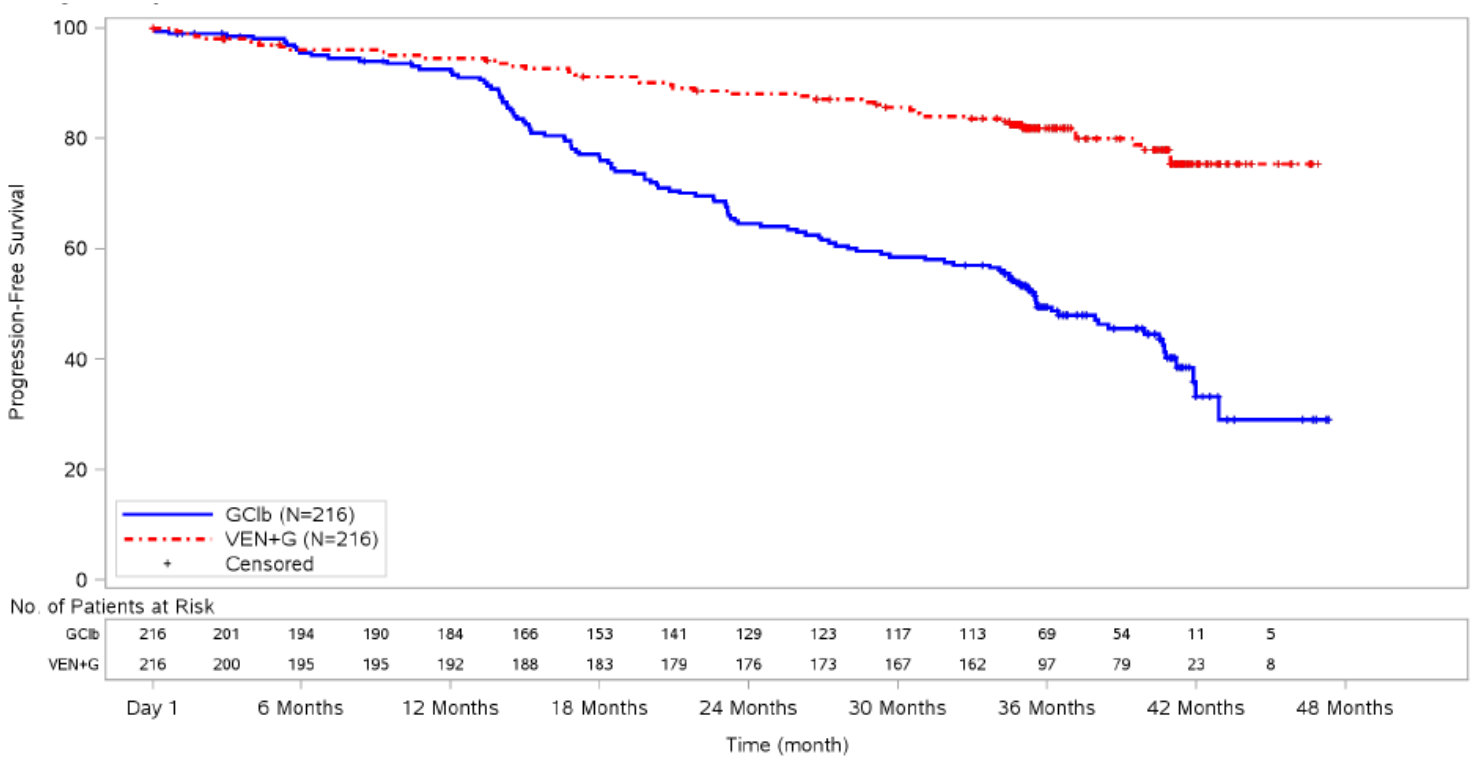
Which PFS model does the committee consider most appropriate?

PFS: reminder of CLL14 results

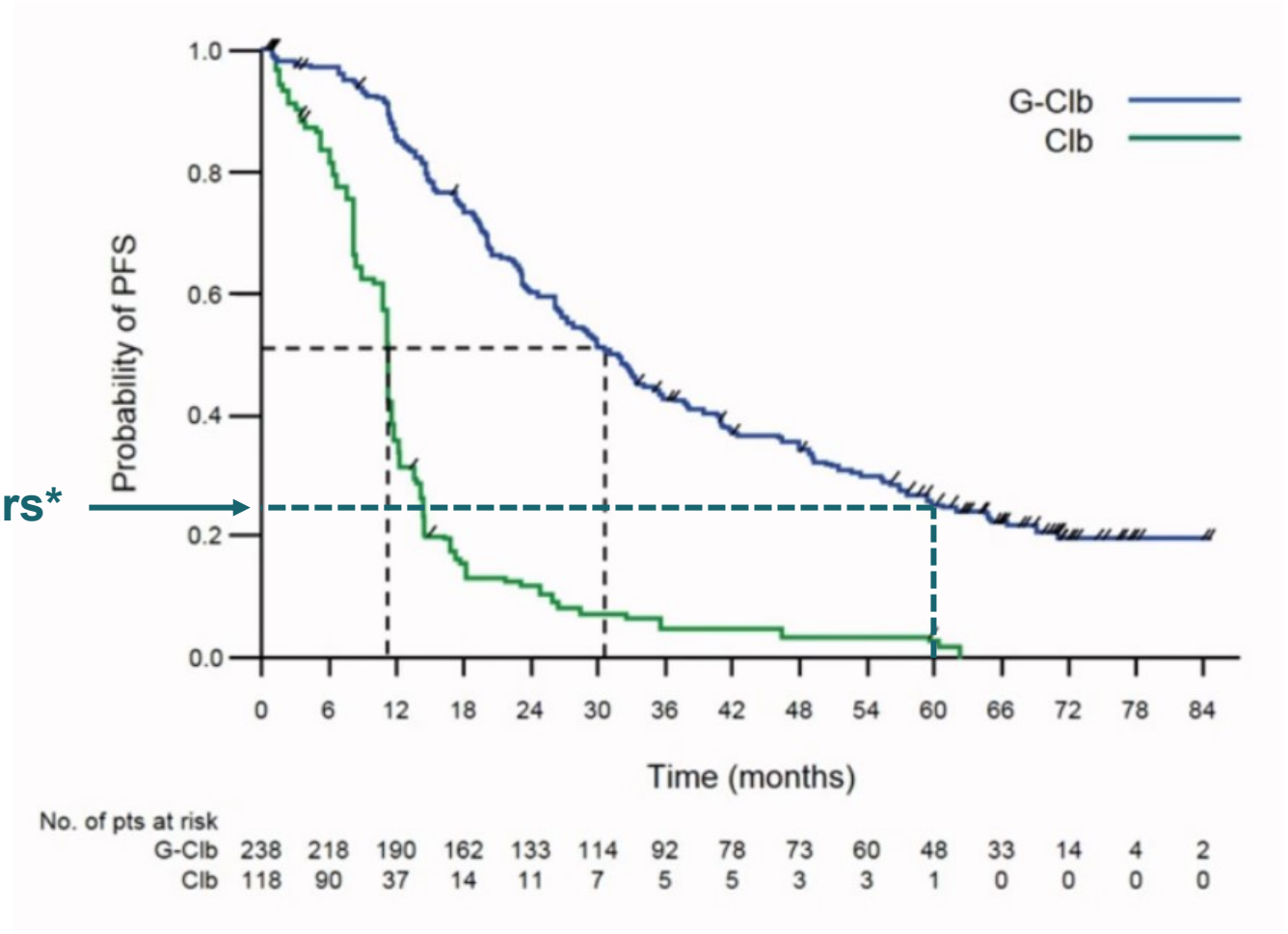


Treatment	Events	Median	KM PFS estimates			Hazard ratio (95% CI)
			1 year	2 year	3 year	
VenG (n=216)	[redacted]	Not reached	[redacted]	88.2%	81.9%	0.31 (0.22 – 0.44)
GClb (n=216)	[redacted]	35.6m	[redacted]	64.1%	49.5%	

PFS: 5-year results from CLL11

Kaplan-Meier PFS plot, CLL11

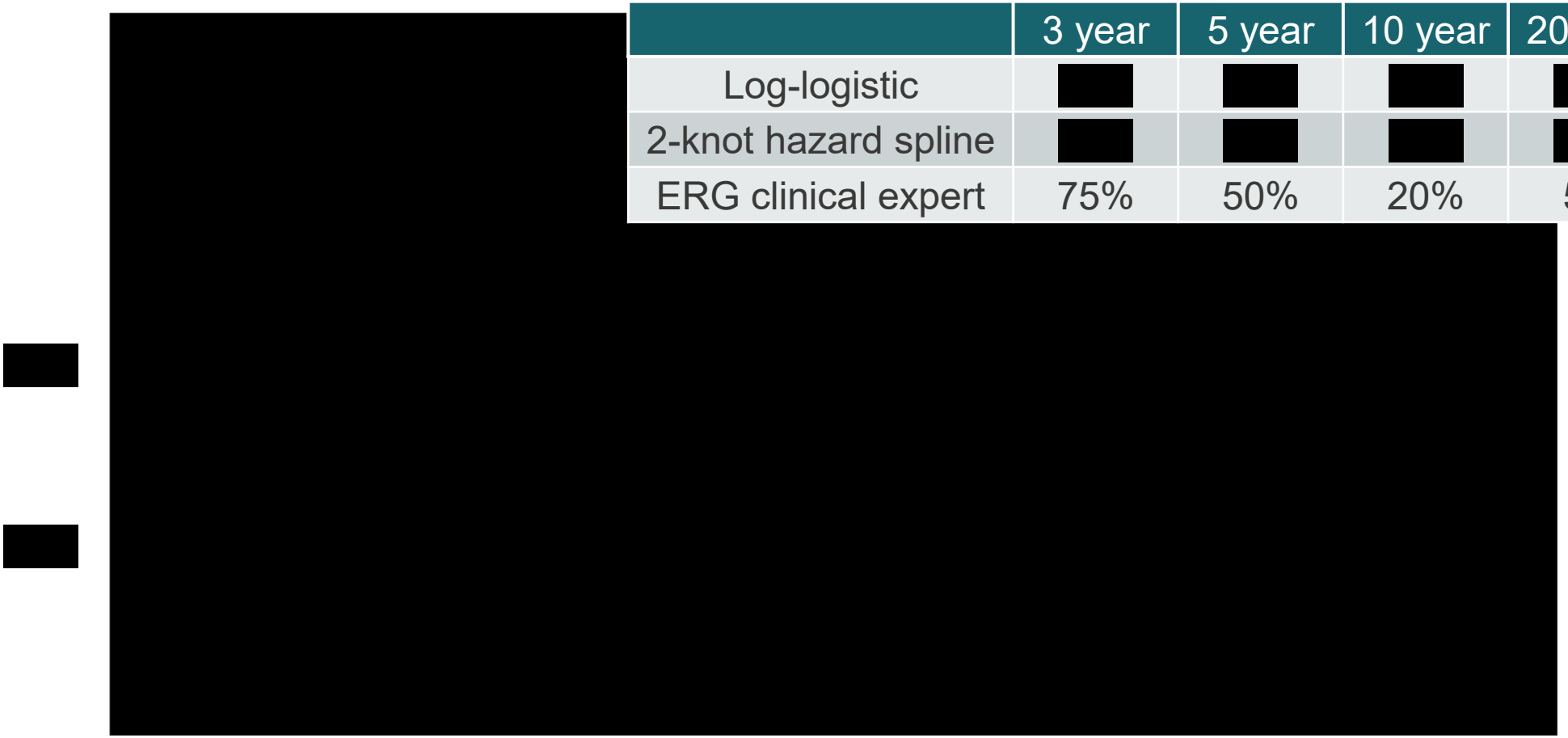
25% at 5 years*



* Includes patients with del(17p)

PFS: Company and ERG-preferred extrapolations

Estimated % non-progressed at each timepoint: **VenG**				
	3 year	5 year	10 year	20 year
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazard spline	[redacted]	[redacted]	[redacted]	[redacted]
ERG clinical expert	75%	50%	20%	5%



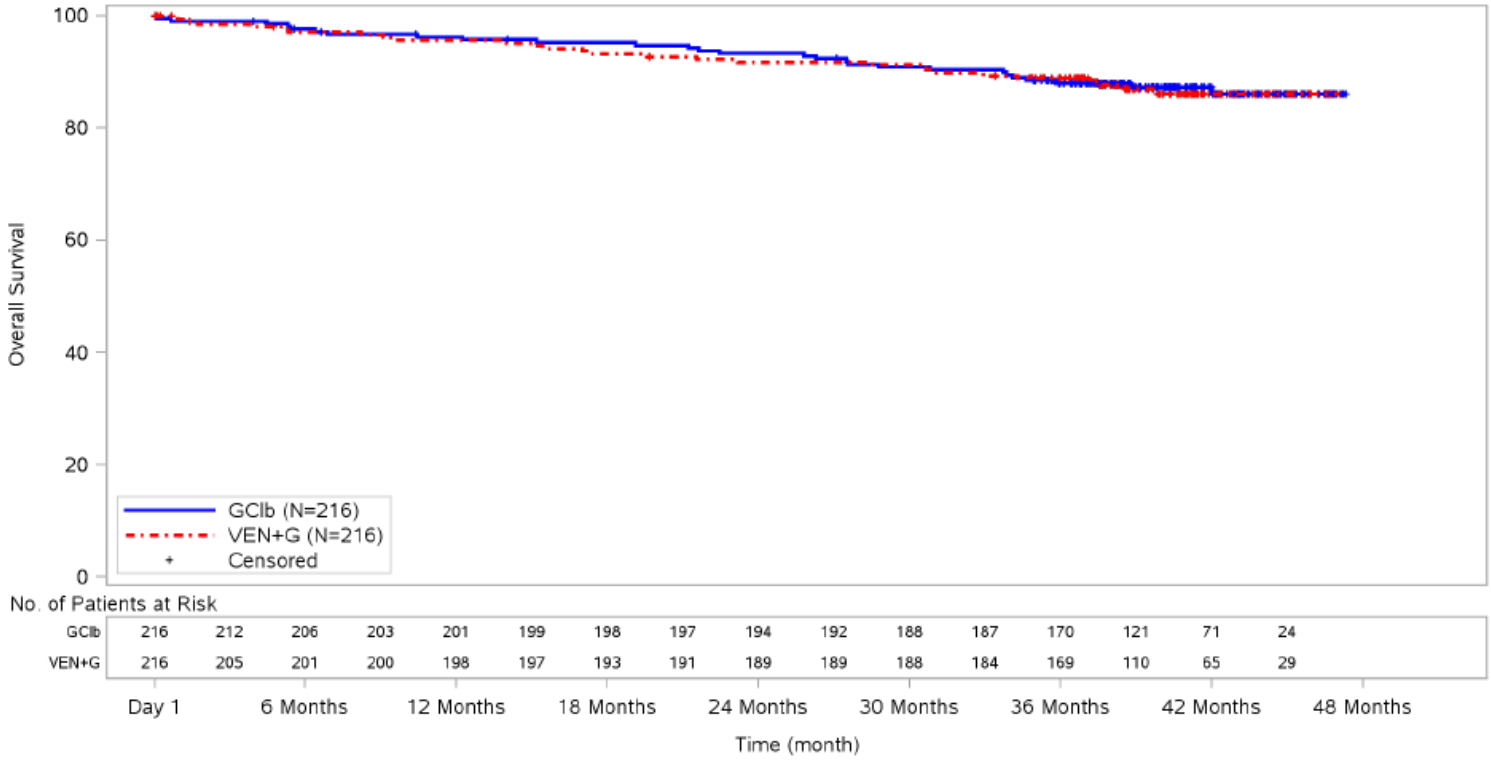
Issue 3: Overall survival extrapolations

- **ERG:** the company's exponential overall survival model is too dependent on background mortality. There is a large difference between the predicted 5-year overall survival for GCIb ([redacted]) compared with the observed CLL11 GCIb data (66%)
- It is implausible that the presence of CLL or comorbidities would not increase mortality over that of the general population
- An exponential model fitted to data from ERIC, modelled beyond 3 years, is more clinically plausible
- **Company**: there are several issues with using ERIC to validate the overall survival extrapolations: 1) it is a RWE evidence study rather than RCT; 2) the available subsequent treatments may differ from current practice; 3) the chlorambucil dosage was lower than CLL14; 4) ERIC included no UK patients
- The CLL14 extrapolations can be expected to be more optimistic than CLL11, as clinical practice has advanced
- **Expert submissions:** the absence of ibrutinib for relapsed/refractory CLL during CLL11 makes its data inappropriate for validating the overall survival curves. Opinions differ as to whether the model of the company or ERG is more plausible

Which OS model does the committee consider most appropriate?

RCT = Randomised controlled trial; RWE = Real-world evidence

OS: reminder of CLL14 results



Treatment	Events	Median	KM OS estimates			Hazard ratio (95% CI)
			1 year	2 year	3 year	
VenG (n=216)	[redacted]	Not reached	[redacted]	91.8%	88.9%	1.03 (0.60 – 1.75)
GClb (n=216)	[redacted]	Not reached	[redacted]	93.3%	88.0%	

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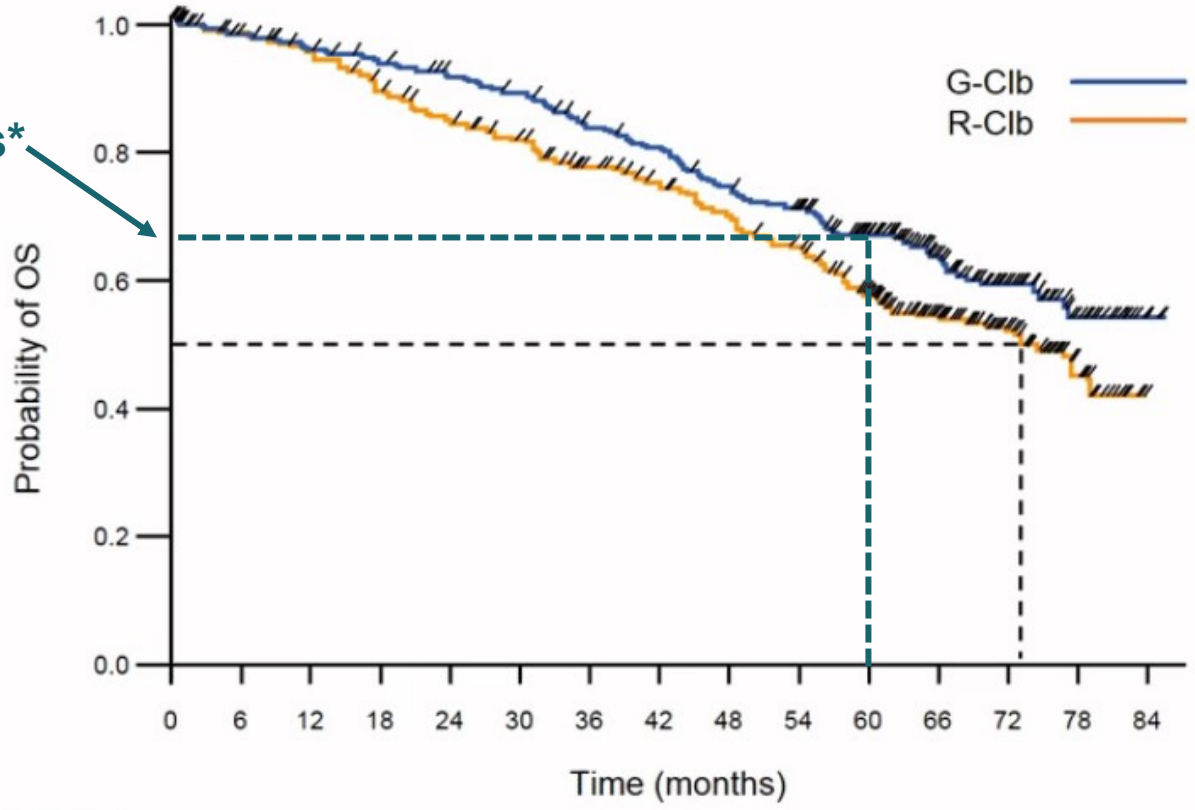
OS: 5-year results from CLL11

Kaplan-Meier OS plot, CLL11

66% at 5 years*



* Includes patients with del(17p)

OS: Company and ERG-preferred extrapolations

- The company and ERG applied the same OS curve for both VenG and GClb in the model due to data immaturity, the impact of innovative later-line treatments on overall survival, and the lack of evidence for an overall survival benefit for VenG

[redacted]

Estimated % alive at each timepoint: **VenG & GClb**				
	3 year	5 year	10 year	20 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
ERIC hazard rate	[redacted]	[redacted]	[redacted]	[redacted]
ERG expert (VenG)		[redacted]	[redacted]	[redacted]
ERG expert (GClb)		[redacted]	[redacted]	[redacted]

VenG KM — GClb KM —
Company extrapolation (exponential) —
ERG extrapolation (exponential fitted to ERIC) —

Low/mod ICER impact

3
2 1

Issue 4b: Time to next treatment extrapolations

- **ERG:** the company's log-logistic model overestimates the proportion of GClb patients that have started second-line treatment (experienced a TTNT event) compared to the CLL11 5-year GClb data. The model is also too reliant on background mortality
- Applying the hazard ratio between TTNT and PFS to the ERG's preferred PFS extrapolation results in a more plausible TTNT extrapolation that is closer to CLL11
- **Company**: clinical input indicates that the log-logistic extrapolation is the most plausible of the tested curves
- Acknowledges that their expert projections support either the company's extrapolation or the ERG's extrapolation
- **Expert submissions:** the CLL11 data should not be used for validating the TTNT extrapolations, as TTNT is likely much shorter for patients in CLL14 due to the availability of better-tolerated targeted therapies
- The ERG's extrapolations give almost identical figures for PFS and TTNT at 20 years for GClb, which is to be expected

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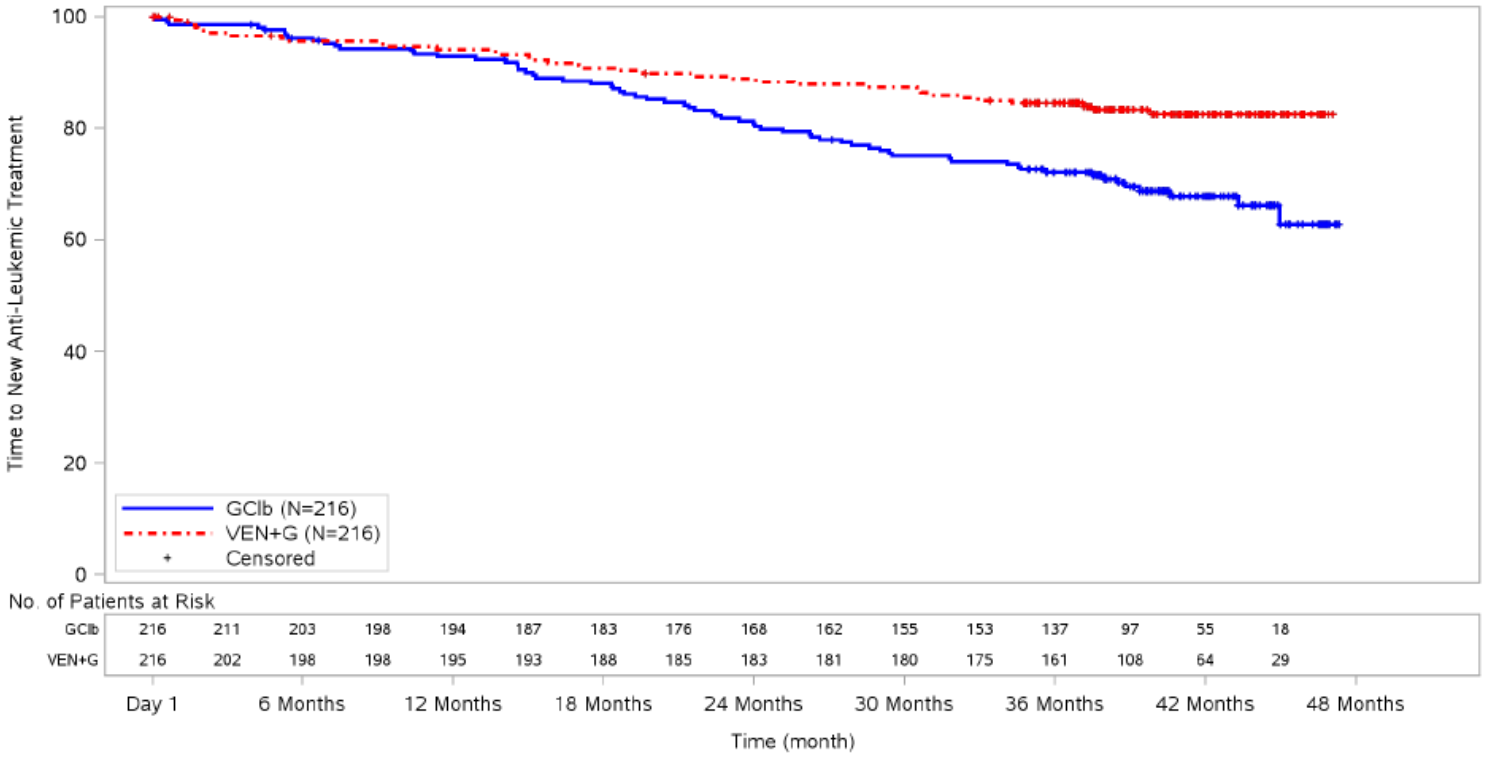
Which TTNT model does the committee consider most appropriate?

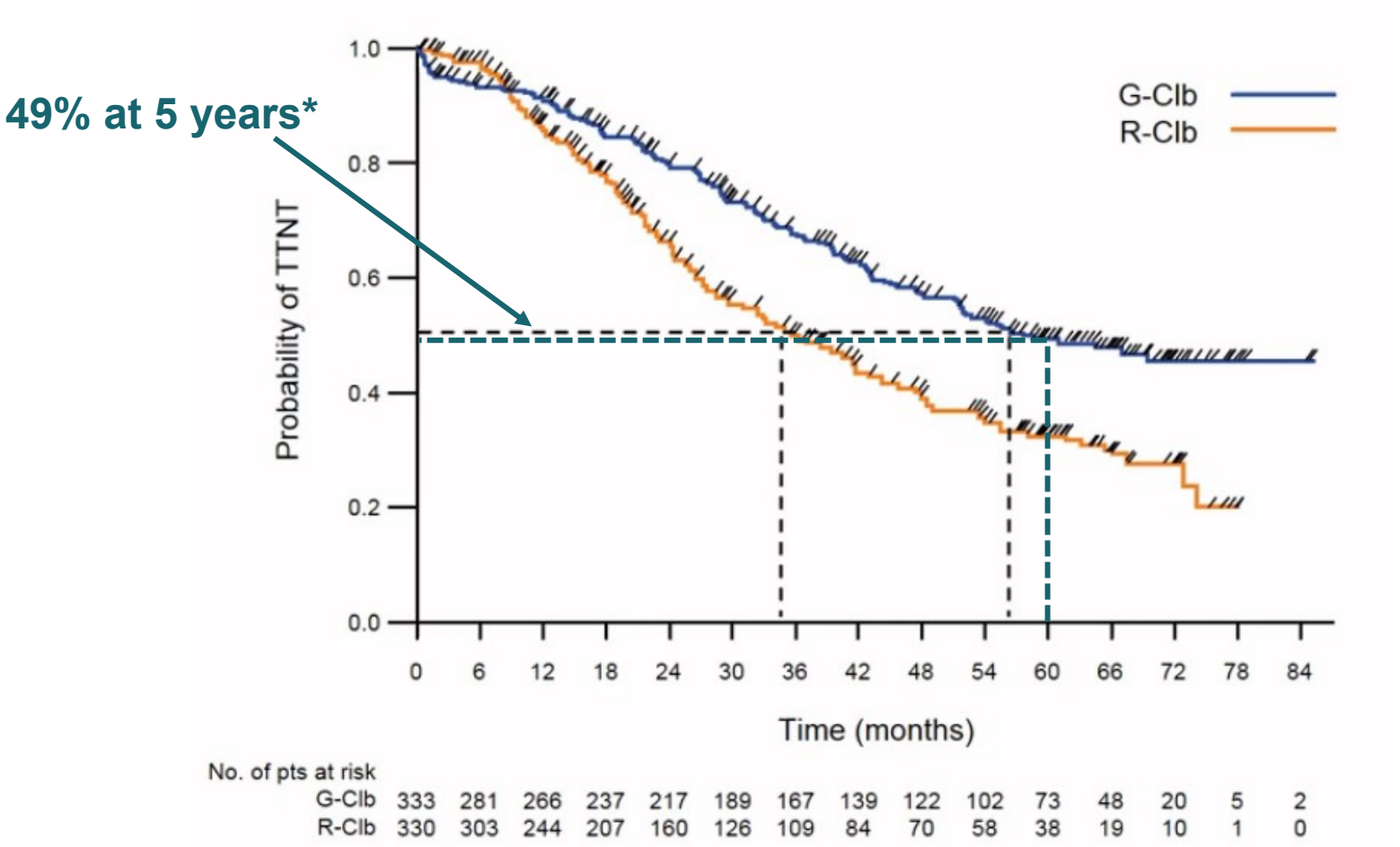
TTNT: CLL14 results



Treatment	Events	Median	KM TTNT estimates			Hazard ratio (95% CI)
			1 year	2 year	3 year	
VenG (n=216)	[redacted]	Not reached	[redacted]	[redacted]	84.5%	0.51 (0.34 – 0.78)
GClb (n=216)	[redacted]	Not reached	[redacted]	[redacted]	72.2%	

TTNT: 5-year results from CLL11

Kaplan-Meier TTNT plot, CLL11



* Includes patients with del(17p)

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TTNT: Company and ERG-preferred extrapolations

Estimated % not on 2L treatment at each timepoint: **VenG**			
	5 year	10 year	20 year
Log-logistic	[redacted]	[redacted]	[redacted]
Hazard ratio on PFS	[redacted]	[redacted]	[redacted]

[redacted]

	VenG	GClb
Kaplan-Meier plot	—	—
Company extrapolations (log-logistic)	—	—
ERG extrapolations (hazard ratio on PFS)	—	—

Summary of company-preferred extrapolations

VenG

GClb

OS —
TTNT —
PFS —

Summary of ERG-preferred extrapolations

VenG

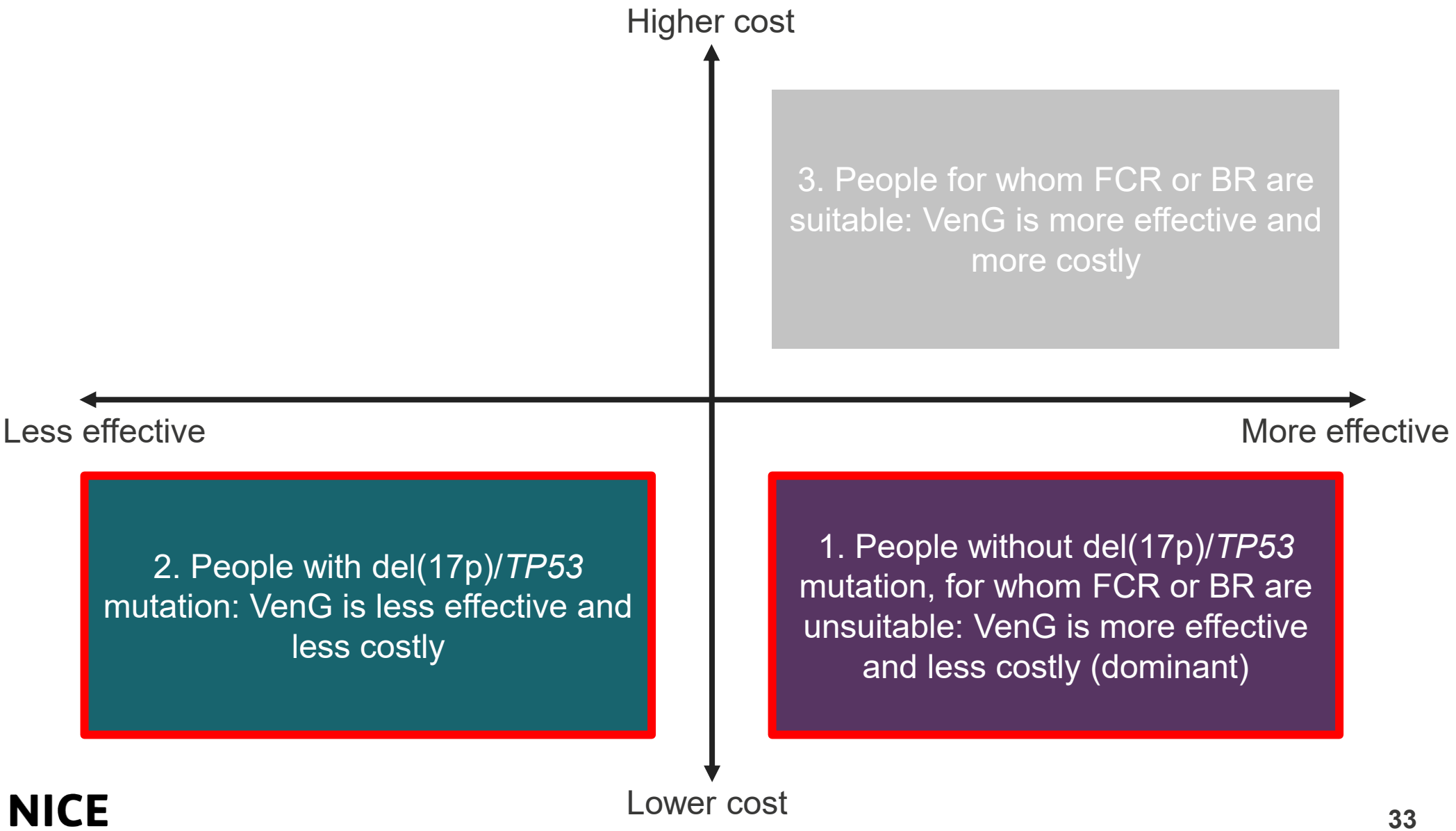
[redacted]

GClb

[redacted]

OS —
TTNT —
PFS —

Issues for discussion: Subgroups 1 and 2



Issue 4a: Subsequent treatment modelling

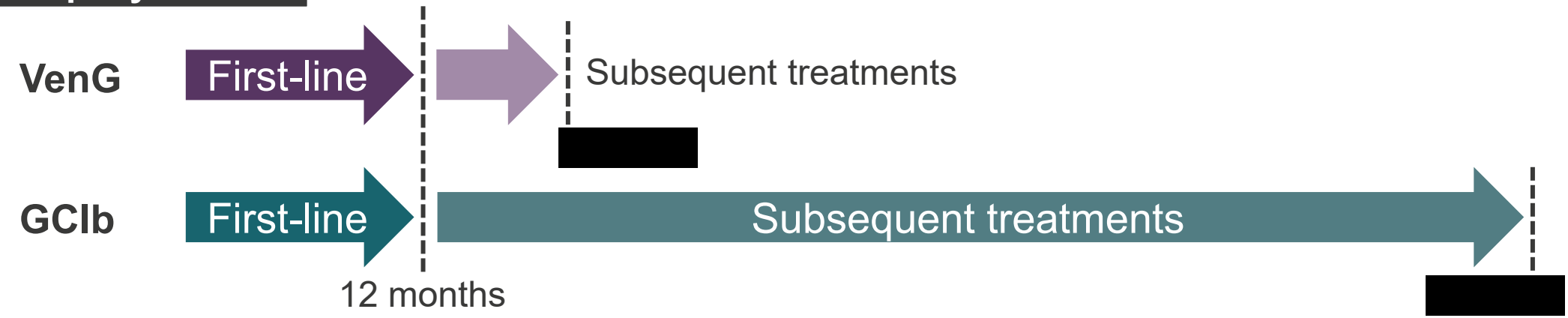
- **Company:** in the base case, subsequent treatment costs are modelled continuously from the start of second-line treatment until death
- It is not feasible to create a treatment sequencing model for the relapsed/refractory setting, as there is a lack of published evidence
- While likely to overestimate subsequent treatment costs, the company considers its approach fair. Restricting R/R treatment costs to 1 subsequent line would not align with clinical practice
- **ERG:** the company's approach is unconventional and does not account for gaps between treatments. The approach is likely to be biased against GClb
- In the company's model, the average time on second-line treatment in the GClb arm is [redacted], compared with a median of [redacted] ([redacted]) of subsequent treatment based on the data from patients in CLL14
- The ERG prefers the company's revised model, where subsequent treatment costs are constrained by estimates from the literature
- **Expert submissions:** it is appropriate to model subsequent treatment costs until death due to the continuous nature of salvage treatments

Should the cost of second-line treatment be assumed to continue until patient death, or be limited based on the literature?

Subsequent treatment modelling: revised model

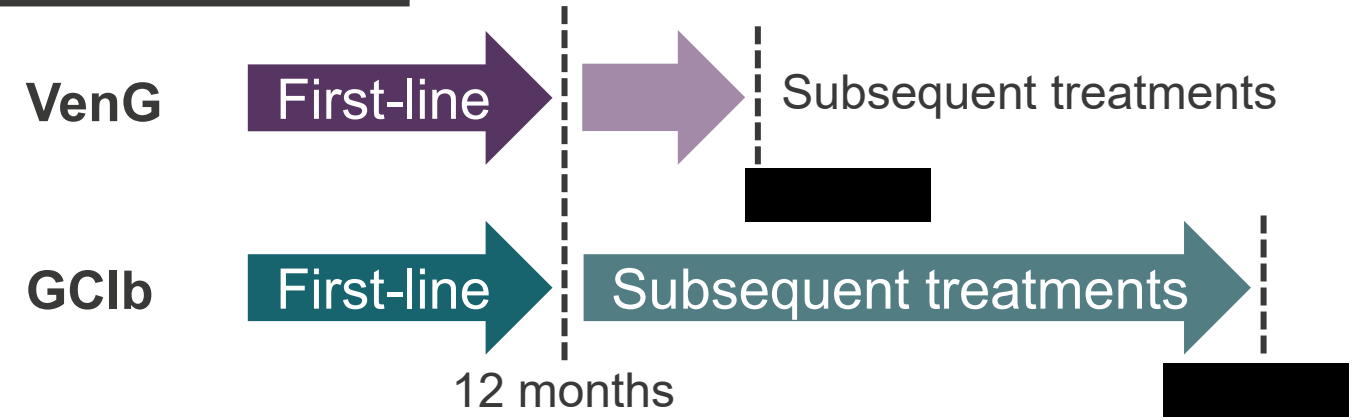
Base-case company model*

Application of drug acquisition costs in the model



Revised company model*

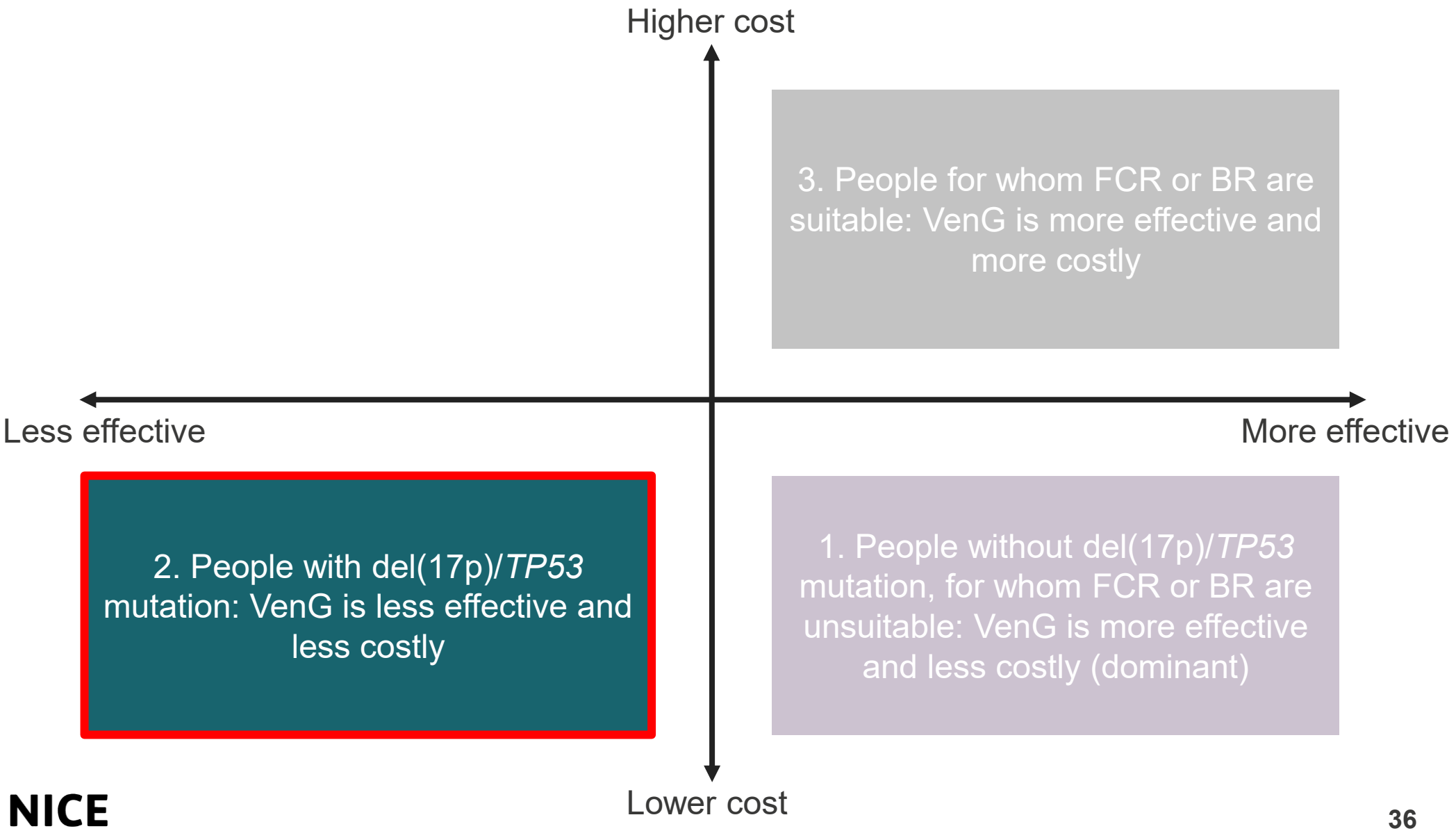
Application of drug acquisition costs in the model



NICE

* People without del(17p)/*TP53* mutation, for whom FCR/BR are unsuitable

Issues for discussion: Subgroup 2



Issue 5: Indirect treatment comparison hazard ratios

	Mato, 2018	Ahn, 2018	Pooled analysis*
PFS hazard ratio	1.515 favouring ibrutinib (95% CI: 0.619, 3.704; p=0.363)	[redacted] (95% CI: [redacted], [redacted]; p=[redacted])	[redacted] (95% CI: [redacted], [redacted]; p=[redacted])
OS hazard ratio	1.189 favouring ibrutinib (95% CI: 0.425, 3.322; p=0.741)	[redacted] (95% CI: [redacted], [redacted]; p=[redacted])	[redacted] (95% CI: [redacted], [redacted]; p=[redacted])

* PFS pooling also includes Woyach et al., excluded by the company from the individual analysis as fewer than 10 patients had del(17p)

- Given the heterogeneity between studies and wide confidence intervals, the **ERG** is unable to conclude which analysis is most reliable.
  - ERG applied the company base case (Mato), in the absence of a better alternative
- The Mato and Ahn populations were likely fitter than that of CLL14, and the results may be biased against VenG. As such, it may be most appropriate to use the Mato figures [redacted]
- **Expert submissions** support using Mato as in the company and ERG base case

Which comparison is most appropriate for decision making?

Issue 6: PFS and OS extrapolations

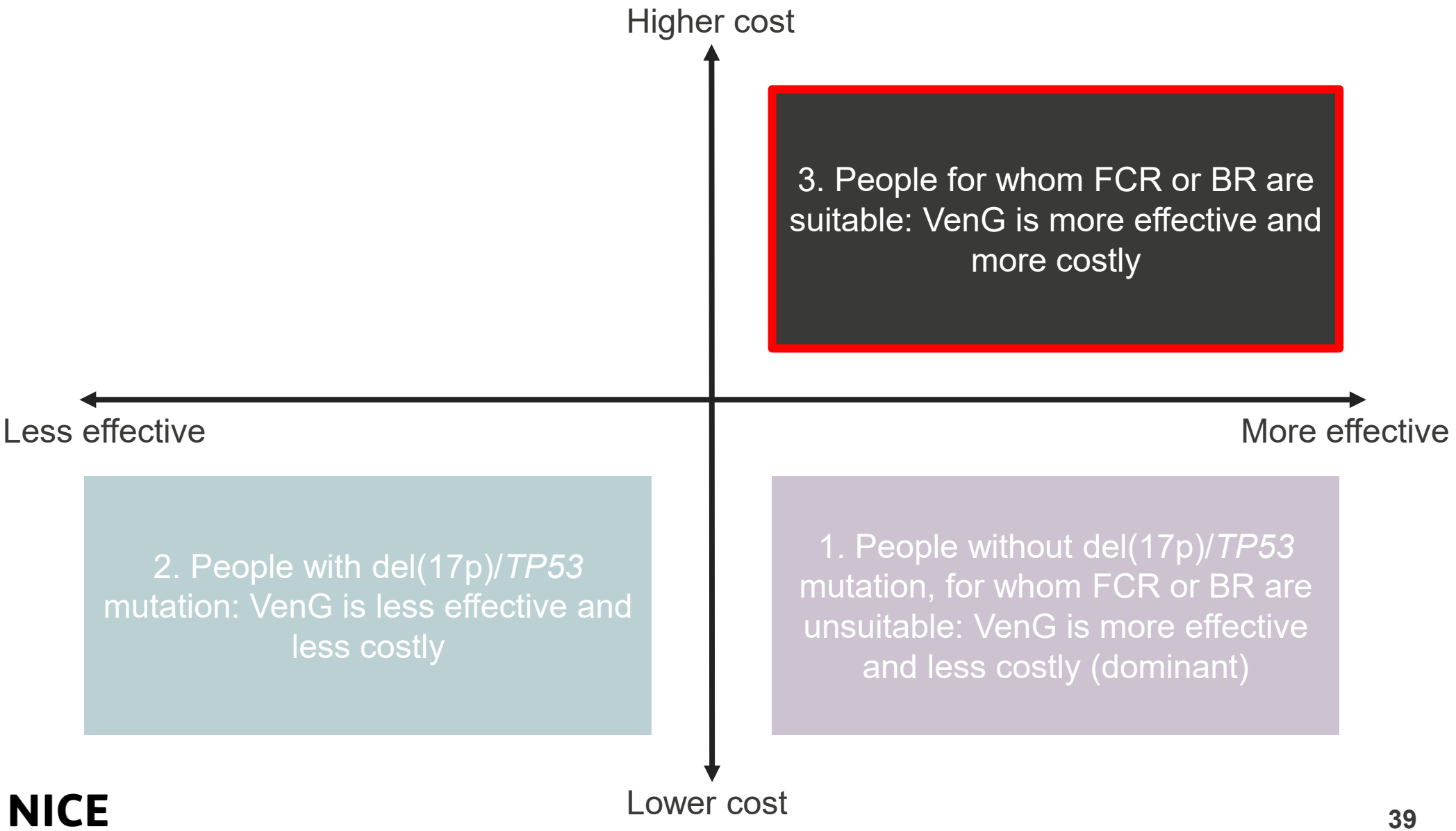
- Extrapolations are highly uncertain due to small patient numbers and immature data
- **Company:** modelled OS differently for the 2 treatment arms by applying the ITC hazard ratio
- The extrapolations result in patients spending little time in post-progression, particularly in the ibrutinib arm. The company considers this consistent with the prognosis of the patient group
- **ERG:** the short time in post-progression is clinically implausible. A 1-knot hazard spline model produces PFS estimates closer to that of the ERG's clinical expert, with patients spending longer in post-progression
- The ERG's 1-knot hazard spline extrapolations produce PFS estimates closer to that of the ERG's clinical expert, and result in patients spending longer in post-progression
- **Expert submissions:** no consensus on the suitability of the company or ERG models

Ibrutinib PFS estimates

Estimate	5 year	10 year	20 year
Company model	[redacted]	[redacted]	[redacted]
ERG model	[redacted]	[redacted]	[redacted]
Company experts	30-60%	Unknown	Unknown
ERG expert	10%	0%	0%

Which models do the committee consider most appropriate?

Issues for discussion: Subgroup 3



Issue 9: Indirect treatment comparison hazard ratios

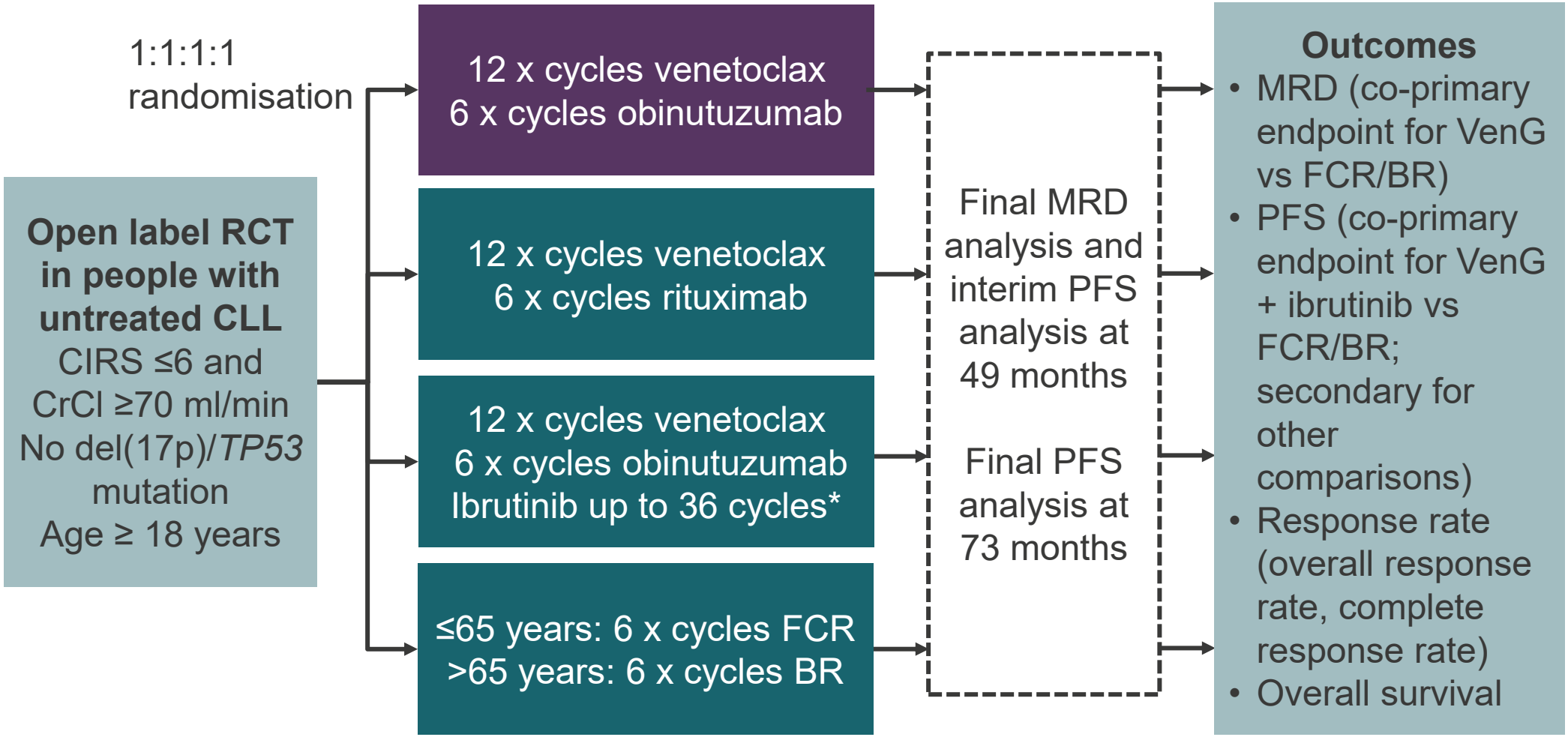
- **Company:** connected VenG to FCR and BR through a network of 9 studies and derived PFS and OS HRs, applying these to the VenG extrapolations from CLL14
- **ERG:** highlighted 3 key areas of uncertainty :
  1. Considerable heterogeneity between studies in age and fitness
  2. PFS and OS hazard ratios resulting from the ITC have wide confidence intervals and are highly sensitive to the choice of studies included in the analysis
  3. The considerable loss of data from using the hazard ratio approach
- The ERG calculated its own PFS and OS hazard ratios, and also applied its preferred 2-knot hazard spline PFS curve

ITC hazard ratios and confidence intervals

	VenG vs FCR: PFS HR (95% CI)	VenG vs BR: PFS HR (95% CI)	VenG vs FCR: OS HR (95% CI)	VenG vs BR: OS HR (95% CI)
Company	0.258 (0.151-0.481)	0.178 (0.109-0.312)	0.622 (0.273-1.789)	0.792 (0.378-1.969)
ERG	[redacted]	[redacted]	[redacted]	[redacted]

Which hazard ratios are most appropriate for the comparison of VenG versus FCR and BR?

CLL13 (n=926) will provide head-to-head data for VenG versus FCR and BR in untreated CLL



* Or until MRD negative, start of new anti-CLL treatment or unacceptable toxicity

Primary completion: **January 2023**
Interim data available: [redacted]

NICE CIRS = Cumulative illness rating scale; CrCl = Creatinine clearance; MRD = Minimal residual disease; PFS = Progression-free survival

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Double counting of patients and inclusion of patients outside of a subgroup within the subgroup evidence	• Entire CLL14 population (which includes people with del(17p)/*TP53* mutation) used to provide clinical effectiveness evidence for people without del(17p)/*TP53* mutation • Patients receiving GClb in CLL14 used to provide evidence for the comparison with ibrutinib in people with del(17p)/*TP53* mutation	Unknown
Proportionality assessments	• Proportional hazards assessments are not always reported by the company – as such hazard ratios may not accurately capture treatment differences	Unknown
Open-label design	• Risk of performance and detection bias	Unknown
Baseline comorbidity imbalances	• Vascular, respiratory, thoracic and mediastinal and psychiatric disorders more common in VenG arm	Infective adverse events likely to be more common in VenG arm
Chlorambucil treatment duration	• Some uncertainty as to the most appropriate chlorambucil treatment duration to apply in model	Unknown

Equality issues, innovation and end of life

Equality issues:

- None raised by company or ERG.
- Patient and professional submissions highlight that restricting VenG to patients for whom FCR or BR are unsuitable would deny younger 'fitter' patients access to a more efficacious, better tolerated treatment.
- The original NICE scope covered the broader population of patients with previously untreated CLL. The company did not initially submit evidence in patients for whom FCR or BR are suitable, but addressed this following technical engagement.

Company on innovation:

- Venetoclax is a first-in-class, oral, selective inhibitor of B-cell lymphoma 2, with a unique targeted mechanism of action that distinguishes it from other therapies.
- VenG increases the range of treatment options for patients for whom FCR or BR are unsuitable, and avoids the need for chemo-immunotherapy.

End of life:

- VenG in untreated CLL does not meet the criterion for short life expectancy, as this population would not normally have a life expectancy of less than 24 months.

CE scenarios (people without del(17p)/*TP53* mutation, for whom FCR/BR are unsuitable)

Versus GCIb. Includes PAS for venetoclax, but not for obinutuzumab or ibrutinib

Scenario (all with ERG's pre-progression off-treatment utility of 0.77)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at £20k/ QALY	NMB at £30k/ QALY
Company base case	-£136,550	0.818	Dominant	£152,904	£161,081
ERG PFS curve	-£131,992	0.454	Dominant	£141,080	£145,624
ERG OS curve	-£69,898	0.774	Dominant	£85,380	£93,121
ERG PFS, OS and TTNT curves	-£127,793	0.454	Dominant	£136,880	£141,424
Subsequent tx costs constrained	-£64,530	0.818	Dominant	£80,884	£89,061
ERG curves, subsequent tx costs constrained (**ERG base case**)	-£57,070	0.454	Dominant	£67,958	£72,501
Technical team-preferred curves (ERG PFS and TTNT curves, company OS curve)	-£145,801	0.454	Dominant	£154,888	£159,432
Technical team-preferred curves, subsequent tx costs constrained	£482	0.454	£1,060	N/A	N/A

Cost effectiveness scenarios (people with del(17p)/*TP53* mutation)

Versus ibrutinib. Includes PAS for venetoclax, but not for obinutuzumab or ibrutinib

Scenario (all with ERG's pre-progression off-treatment utility of 0.77)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (SW quadrant*)	NMB at £20k/ QALY	NMB at £30k/ QALY
Company base case	-£280,896	-0.351	£799,551	£273,870	£270,357
HRs from Ahn	-£464,090	-2.437	£190,398	£415,341	£390,966
Equal efficacy (HRs = 1)	-£211,754	0.192	Dominant	£215,603	£217,527
HRs from pooled data	-£370,639	-1.378	£268,873	£343,069	£329,284
HR CI lower bound for OS & PFS	-£513,444	-3.052	£168,252	£452,411	£421,895
ERG PFS curve	-£188,767	-0.404	£467,683	£180,695	£176,659
ERG OS curve	-£247,609	-0.300	£825,643	£241,611	£238,612
ERG TTNT curve	-£229,562	-0.351	£653,432	£222,536	£219,023
ERG PFS, OS and TTNT curves	-£167,893	-0.363	£462,327	£160,630	£156,998
Subsequent tx costs constrained	-£281,782	-0.351	£802,073	£274,756	£271,243
ERG curves, subsequent tx costs constrained (**ERG base case**)	-£199,622	-0.363	£549,699	£192,359	£188,727

* Other than equal efficacy scenario

Cost effectiveness scenarios (people for whom FCR or BR are suitable)

Includes PAS for venetoclax, but not for obinutuzumab or ibrutinib

Revised ERG PFS curve and pre-progression off-treatment utility applied for all ERG scenarios

		ICERs: vs. FCR	vs. BR
	Company:	£32,669	£36,768
ERG base-case PFS hazard ratio (HR)	ERG base-case OS HR	£47,494	£67,445
	OS HR of 1	£141,738	£107,376
	ERG OS HR CI upper bound	£21,845	£24,897
	ERG OS HR CI lower bound	£459,089	£259,764
ERG PFS HR confidence interval (CI) upper bound	ERG base-case OS HR	£41,967	£58,686
	OS HR of 1	£103,024	£86,889
	ERG OS HR CI upper bound	£20,547	£23,580
	ERG OS HR CI lower bound	£209,454	£166,063
ERG PFS HR CI lower bound	ERG base-case OS HR	£56,736	£82,839
	OS HR of 1	£259,960	£151,162
	ERG OS HR CI upper bound	£23,365	£26,861
	ERG OS HR CI lower bound	Dominated	£820,343